RESULTS

In vitro quantitative studies

In vitro quantitative analysis of cefoxitin

Amount of cefoxitin in six vials of Cefoxin® and six vials Cefxitin® were assayed in duplicate by HPLC technique. Individual amount of cefoxitin in each vial and mean amount are shown in Table 7. Mean amount of cefoxitin was slightly lower for the generic Cefxitin® with the mean value of 1061.43 ± 28.42 mg compared to 1077.05 ± 17.10 mg for Cefoxin® (P = 0.28).

Table 7 Amount of cefoxitin measured in 6 vials of Cefoxin® and 6 vial of Cefxitin®.

Vial No.	Amount of cefoxitin (mg)	
	Cefoxin®	Cefxitin®
1	1088.38	1087.98
2	1101.99	1100.61
3	1084.75	1028.48
4	1062.97	1035.79
5	1064.05	1053.99
6	1060.14	1061.71
mean	1077.05	1061.43
SD	17.10	28.42
P value	-	0.28[a]

[a] compared with Cefoxin®

***In vitro* quantitative analysis of ceftazidime**

Amount of ceftazidime in six vials of Fortum® and six vials of Cef-4® were assayed in duplicate by HPLC technique. Individual amount of ceftazidime in each vial and mean amount are shown in Table 8. Mean amount of ceftazidime was slightly lower for the generic Cef-4® with the mean value of 1030.16 ± 24.37 mg compared to 1056.00 ± 14.99 mg for Fortum® (P = 0.05).

Table 8 Amount of ceftazidime measured in 6 vials of Fortum® and 6 vials of Cef-4®.

Vial No.	Amount of ceftazidime(mg)	
	Fortum®	Cef-4®
1	1045.53	1003.98
2	1039.53	1073.52
3	1052.46	1029.39
4	1050.48	1013.18
5	1068.87	1022.84
6	1079.12	1038.07
mean	1056.00	1030.16
SD	14.99	24.37
P value	-	0.05[a]

[a] compared with Fortum®

Bioequivalence Testing and Pharmacokinetic Studies

Bioequivalence and pharmacokinetics of cefoxitin following intramuscular administration of Cefoxin® and Cefxitin®

In this randomized cross-over study, twelve healthy volunteers (six males and six females) were given 1000 mg of intramuscular cefoxitin in the formulation of Cefoxin® and Cefxitin®. All subjects completed the study without any serious adverse effect. Individual and mean demographic data of subjects are presented in Table 1.

The mean serum concentration-time profiles of cefoxitin are shown in Table 9 and Fig 5. There was no significant difference in the mean concentration-time profile between the generic Cefxitin® and the standard Cefoxin® formulation. Mean pharmacokinetic parameters derived from individual concentration-time curves are shown in Table 10. The calculated parameters including V_d, K_a, T_{max}, C_{max}, $t_{1/2}$, Cl, K_e and $AUC_{0-\infty}$ of both cefoxitin preparations did not reach statistically significant differences. Both Cefxitin® and Cefoxin® reached the maximum concentrations at about 0.6 hr after intramuscular administration. However, the T_{max} was slightly faster for Cefxitin® with the mean value of 0.59 ± 0.29 hr compared to 0.67 ± 0.29 hr for Cefoxin®. At this time point, the mean peak serum level of Cefoxitin was slightly higher for Cefxitin® than Cefoxin® preparations (28.21 ± 10.90 μg/ml vs 26.34 ± 8.75 μg/ml). Cefoxin® and Cefxitin® had comparable mean absorption and elimination rate constants (3.54 ± 1.67 vs 3.81 ± 1.50 hr^{-}, and 0.86 ± 0.18 vs 0.91± 0.23 hr^{-1}, respectively). The elimination half-life and clearance were calculated to be 0.84 ± 0.18 hr and 340.75 ± 94.86 ml/min for Cefoxin® vs 0.80 ± 0.18 hr and 350.92 ± 103.44 ml/min for Cefxitin®, respectively. The mean value of $AUC_{0-\infty}$ was slightly lower for Cefxitin® (50.83 ±

13.19 μg.hr/ml) than Cefoxin® (52.57 ± 14.91 μg.hr/ml). The relative bioavailability (F_{rel}) of Cefxitin® was 98 ± 15 % of the innovator Cefoxin® as calculated from $AUC_{0-\infty}$.

Table 9 Mean plasma concentrations (± SD) of cefoxitin at each sampling times after intramuscular administration of 1000 mg of Cefoxin® and Cefxitin® in twelve healthy volunteers.

Time (hr)	Plasma concentrations (μg/ml)		P value
	Cefoxin®	Cefxitin®	
0.00	0	0	-
0.17	17.05 ± 10.03	18.81 ± 11.11	0.45
0.33	21.89 ± 10.89	26.03 ± 12.90	0.25
0.50	24.67 ± 9.76	26.94 ± 11.44	0.42
0.75	24.56 ± 8.19	23.63 ± 7.90	0.59
1.00	21.18 ± 6.09	20.85 ± 6.21	0.82
1.50	15.92 ± 4.73	15.28 ± 4.13	0.55
2.00	11.51 ± 3.86	11.16 ± 3.43	0.64
3.00	5.86 ± 2.77	5.12 ± 2.36	0.19
4.00	2.97 ± 1.39	2.44 ± 1.37	0.16
6.00	1.12 ± 0.70	0.93 ± 0.46	0.15

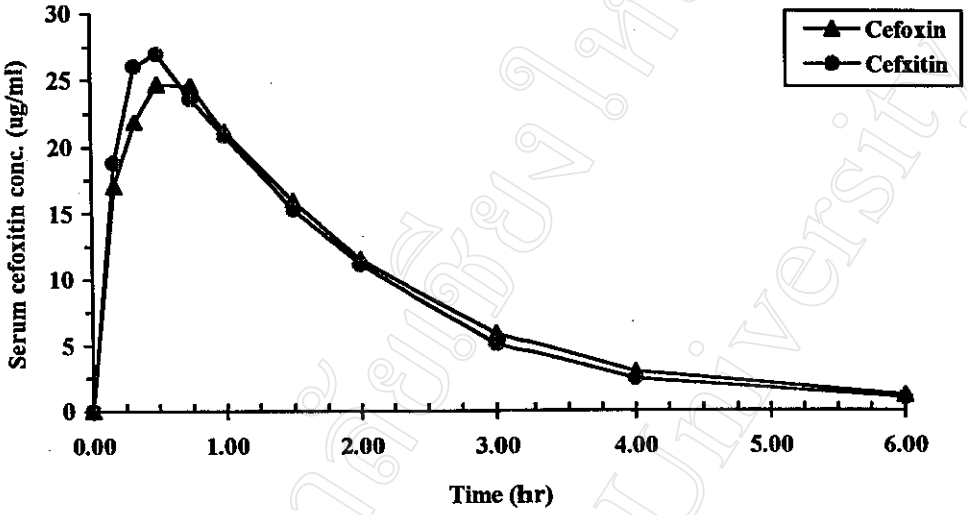

Figure 5 Mean plasma concentration-time curves after 1000 mg intramuscular dosage of Cefoxin® and Cefxitin®.

Table 10 Comparison of cefoxitin pharmacokinetic parameters after intramuscular administration of 1000 mg Cefoxin® and Cefxitin® in twelve healthy volunteers. (Data are expressed as mean ± SD).

Parameters	Cefoxin®	Cefxitin®	P value
V_d (L)	24.21 ± 5.92	24.42 ± 9.59	0.93
K_a (hr^{-1})	3.54 ± 1.67	3.81 ± 1.50	0.44
T_{max} (hr)	0.67 ± 0.29	0.59 ± 0.29	0.18
C_{max} (μg/ml)	26.34 ± 8.75	28.21 ±10.90	0.45
$t_{1/2}$ (hr)	0.84 ± 0.18	0.80 ± 0.18	0.63
Cl (ml/min)	340.75 ±94.86	350.92 ± 103.44	0.51
K_e (hr^{-1})	0.86 ± 0.18	0.91 ± 0.23	0.59
$AUC_{0-\infty}$ (μg.hr/ml)	52.57 ± 14.91	50.83 ± 13.19	0.48
F_{rel} (%)	-	98 ± 15	-

Bioequivalence and pharmacokinetics of ceftazidime following intramuscular administration of Fortum® and Cef-4®.

Twelve healthy volunteers (six males and six females) were given 1000 mg of intramuscular ceftazidime in the formulation of Fortum® and Cef-4® in randomized cross-over fashion. All subjects completed the study without any serious adverse effect. Individual and mean demographic data of subjects are presented in Table 2.

The mean serum concentration-time profiles of ceftazidime are shown in Table 11 and Fig 6. There was no significant difference in the mean concentration-time profile between the generic Cef-4® and the standard Fortum® formulations. Mean pharmacokinetic parameters derived from individual concentration-time curve of subjects are shown in Table 12. The calculated parameters including V_d, K_a, T_{max}, C_{max}, $t_{1/2}$, Cl, K_e and $AUC_{0-\infty}$ of the two ceftazidime preparations were not significantly different. Both Fortum® and Cef-4® reached the maximum concentrations at about 1.2 hr after intramuscular administration. Fortum® yielded slightly higher maximum serum ceftazidime concentration than Cef-4® preparations (31.38 ± 9.23 μg/ml vs 28.78 ± 6.63 μg/ml). Fortum® and Cef-4® had comparable mean absorption and elimination rate constants (1.92 ± 0.83 vs 1.92± 0.88 hr^{-1}, and 0.39 ± 0.11 vs 0.37± 0.12 hr^{-1}, respectively). The half-life of elimination and clearance were calculated to be 1.88 ± 0.48 hr and 132.46±30.75 ml/min for Fortum® vs 1.97 ± 0.56 hr and 137.03 ± 29.99 ml/min for Cef-4® (P=0.61 and P=0.39, respectively). The mean value of $AUC_{0-\infty}$ was slightly lower for Cef-4® (128.44 ± 35.16 μg.hr/ml) than Fortum® (131.94 ± 29.86 μg.hr/ml). The relative bioavailability (F_{rel}) of Cef-4® was 98 ± 12 % of Fortum®.

Table 11 Mean plasma concentrations (± SD) of ceftazidime at each sampling times after intramuscular administration of 1000 mg of Fortum® and Cef-4® in twelve healthy volunteers.

Time (hr)	Plasma concentrations (μg/ml)		P value
	Fortum®	Cef-4®	
0.00	0	0	-
0.08	7.70 ± 6.50	6.70 ± 4.89	0.18
0.25	15.66 ± 9.63	15.18 ± 7.71	0.91
0.50	24.51 ± 10.16	22.42 ± 8.22	0.21
0.75	26.81 ± 10.22	25.05 ± 7.51	0.25
1.00	30.42 ± 10.62	27.23 ± 7.50	0.13
1.50	29.86 ± 8.63	27.79 ± 6.41	0.21
2.00	26.79 ± 6.99	25.45 ± 6.06	0.14
3.00	19.57 ± 4.32	18.58 ± 5.30	0.16
4.00	14.44 ± 3.31	13.94 ± 4.10	0.51
6.00	7.25 ± 1.71	7.03 ± 2.10	0.71
8.00	3.76 ± 1.24	3.78 ± 1.30	0.97

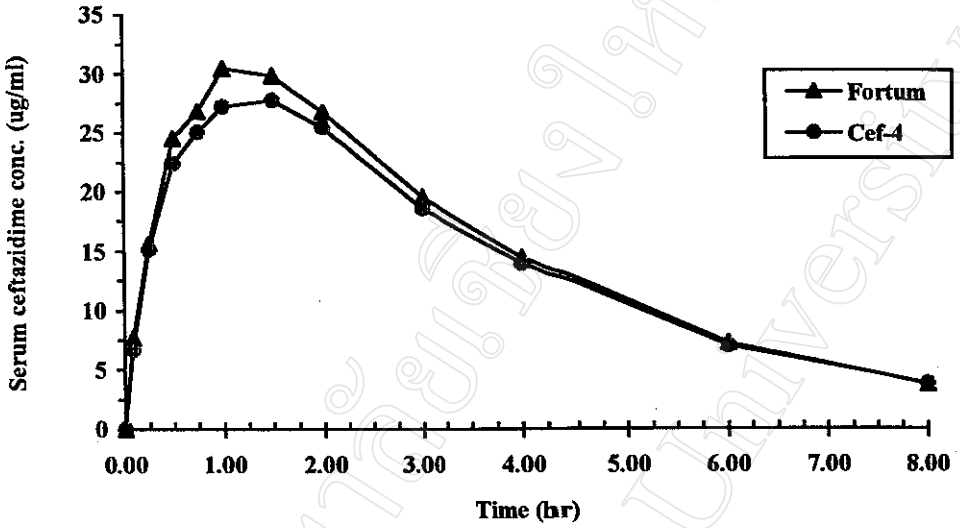

Figure 6 Mean plasma concentration-time curves after 1000 mg intramuscular dosage of Fortum® and Cef-4®.

Table 12 Comparison of ceftazidime pharmacokinetic parameters after intramuscular administration of 1000 mg Fortum® and Cef-4® in twelve healthy volunteers. (Data are expressed as mean ± SD).

Parameters	Fortum®	Cef-4®	P value
V_d (L)	21.72 ± 7.24	22.84 ± 5.13	0.43
K_a (hr^{-1})	1.92 ± 0.83	1.92 ± 0.88	0.97
T_{max} (hr)	1.21 ± 0.39	1.23 ± 0.47	0.65
C_{max} (μg/ml)	31.38 ± 9.23	28.78 ± 6.63	0.08
$t_{1/2}$ (hr)	1.88 ± 0.48	1.97 ± 0.56	0.61
Cl (ml/min)	132.46 ± 30.75	137.03 ± 29.99	0.39
K_e (hr^{-1})	0.39 ± 0.11	0.37 ± 0.12	0.76
$AUC_{0-\infty}$ (μg.hr/ml)	131.94 ± 29.86	128.44 ± 35.16	0.52
F_{rel} (%)	-	98 ± 12	-